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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/770,294	02/02/2004	Andrew D. Miller	YOUZ 2 00059-2	1414

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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/770,294	MILLER ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-75* is/are pending in the application.

4a) Of the above claim(s) *71-75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 28, 2006 has been entered. Claims 1-22 have been cancelled. Claims 71-75 have been added.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Restriction/Election

3. Newly submitted claims 71-75 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Newly submitted claims 71-75, drawn to a method for delivering a therapeutic agent to one or more cells and are distinct from examined claims 23-70, drawn to a method of treating a genetic disorder or condition or disease in a patient. Since applicant has received an action on the merits for the originally presented invention, the invention as set forth in claims 23-70 has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 71-75 are withdrawn

from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Rejection Maintained

4. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims 23-70 for the reasons set forth on pages 3-6, paragraph 4 of the Final Office Action.

The rejection was on the grounds that the claims are directed to a method for treating a genetic disorder or condition or disease in a patient in need of treatment comprising administering an effective amount of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group, wherein the head group is more positive than the head group of DC-Chol; further wherein the head group is a straight chain polyamine; further wherein two or more of the amine groups of the polyamine are separated by an ethylene group.

The claims broadly encompasses gene therapy, wherein the claimed method of treating a genetic disorder or condition or disease, is treated by administering a cationic lipid compound admixed with or associated with a nucleotide sequence.

The specification teaches that the compound of the invention is used in gene therapy, especially gene transfer (page 1). The specification teaches that one aspect of gene therapy involves the introduction of foreign nucleic acid into cells so that it is expressed protein may carry out a desired therapeutic function (page 1). The specification teaches that this type of therapy includes the insertion of TK, TSG or ILG gene to treat cancer, the insertion of the CFTR gene to treat cystic fibrosis, the insertion of the NGF, TH or LDL genes to treat neurodegenerative and cardiovascular disorders, the insertion of the IL-1 antagonist gene to treat rheumatoid arthritis, the insertion of the HIV antigens and the TK genes to treat AIDS and CMV infections, the insertion of antigens and cytokines to act as vaccines and the insertion of β-globin to treat haemoglobinopathic conditions such as thalassaemias (page 1). There are no working examples in the instant specification to guide the skilled artisan in practicing the claimed method.

The state of the art for gene therapy as discussed by Vile et al *(Gene Therapy, Vol. 7, pp. 2-8, 2000)* is unpredictable. Vile et al teach that the problems in which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. Vile et al teach that there is already a battery of genes that we know are very effective in killing cells and if these genes can be expressed at the right site and at appropriate levels therapy may be occur (page 2). However, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Vile et al teach that whatever its mechanism, no single genes can be a serious contender unless it has

a demonstrable bystander effect (page 2, right column) and the requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column). Vile et al teach that a genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. Vile et al teach that in truth, no such systemically targeted vectors exist yet. Vile et al teach that injection of vectors into the bloodstream for the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column). In addition, Rochlitz C. F. *(Swiss Medicine Weekly, 131:4-9, 2001)* teaches that none of the more than one hundred clinical studies performed so far had formally proven efficacy of the approach (gene therapy) in any human disease. Rochilitz teaches that although anecdotal reports of tumor responses are becoming more frequent in several human malignancies, the situation has not changed dramatically." (see page 8, bottom of page). Rochlitz teaches that the main problems are still the lack of vectors with high transduction efficiency *in vivo*, the low tumor specificity of available systems, and our incomplete knowledge of molecular tumor pathology" (pages 8-9).

Thus, as taught above the state of the art regarding gene therapy is considered highly unpredictable. Furthermore, it would take one skilled in the art an undue amount of experimentation to determine what route of administration (e.g. intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) would result in a therapeutic response using a recombinant virus, lentivirus, adenovirus, retrovirus or bacterium comprising the nucleic acid encoding the antigen. The state of the art regarding the route of administration for gene therapy as exemplified by Verma et al, (*Nature, Vol. 389, No. 6648, pages 239-242, 1997)*, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Therefore, the skilled artisan at the time the invention was made recognized the lack of predictability of the nature of the art and state of the prior art to which the instant invention pertains. .Also, such disclosures clearly indicate that the amount of direction or guidance presented in the specification is limited, and would not permit a person skilled in the art to use the invention without undue experimentation at the time the invention was made.

In view of the lack of predictability of the art to which the invention pertains, the lack of established clinical protocols for effective gene therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for treating a genetic disorder, or condition or disease in a patient.

Applicant's Arguments

A) Applicant urges that the specification as originally filed and the supporting documents provided in the March 31, 2006 response provide evidence that is reasonably predictive that the claimed methods are effective for treating a genetic disorder or condition in a patient. Applicant urges that the specification indicates that non-viral transfer systems using liposomes are known and that efficacy of cationic liposomes has been illustrated both *in vitro* and *in vivo*. Applicant refers to page 1, lines 24-30 of the instant specification.

B) Applicant urges that the application and references cited in the March 31, 2006 response show that the claims are enabled. Applicant urges the application provides numerous examples of *in vitro* and *in vivo* gene delivery assay studies. Applicant urges that *in vitro* assays measure gene delivery activity as a function of chloramphenicol acetyl transferase (CAT) activity or expression. Applicant urges that Alton et al disclose that evaluating CAT expression is a suitable way to evaluate therapeutic potential. Applicant urges that Dorin (Gene Therapy, 1996) states that "an attraction of gene therapy is the symptoms can be expected to be ameliorated despite an incomplete understanding of disease pathogenesis". Applicant urges that Dorin, 1996 demonstrated that only small amounts of gene expression are necessary to provide a therapeutic effect. Applicant urges that Dorin discloses that "50% of the normal level of gene

expression is sufficient to prevent disease and that production of 0.5 to 6% of the normal level of enzyme activity was sufficient to result in complete disappearance of lysosomal storage lesions in the liver and spleen of mutant mice".

C) Applicant urges that Dr. Keller's declaration demonstrate that the current compounds are suitable for delivering genes to cells as evidenced by evaluating CAT expression.

Examiner's Response to Applicant

Applicant's arguments filed September 28, 2006 have been fully considered but they are not persuasive.

It is the Examiner's position that the specification is not enabled for the claimed method.

A) To address Applicant's comments regarding the instant specification, for example page 19 and figures 24 and 25, it should be noted that the figure 24 relates to *in vitro* data as a result of studies performed using cystic fibrosis epithelial cells. Figure 25 of the instant specification recites that the *in vivo* data was obtained by the intranasal instillation of cationic liposome/plasmid DNA complexes in to the lungs of female BALB/c mice. Thus, the instant specification teaches the delivery of cationic liposomes to the lungs of BALB/c mice. This assay determines gene delivery activity and not treatment of cystic fibrosis or any other genetic disorder, condition or disease (see page 16 of the instant specification). The instant specification does not include information on

how the cationic liposomes were used to treat mice with cystic fibrosis or any other genetic disorder, condition or disease. Therefore, the instant specification is not enabled for treating a genetic disorder, condition or disease in a patient.

B) It must be remembered that Applicant must be enabled for the claimed invention at the time of filing. It must also be remembered the lack of established clinical protocols for effective gene therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods. Thus, Applicant must provide evidence which is reasonably predictive that the claimed methods are effective for treating a genetic disorder, or condition or disease in a patient.

To address Applicant's comments regarding Dorin, Dorin et al merely demonstrates that there is a relationship between Cftr gene expression, chloride ion transport and survival are non linear (page 798, first column).

To address Applicant's comments regarding, Alton et al merely demonstrates that gene expression is greater and lasts longer in adult mice compared with your mice *in vivo*. This article merely suggests that cationic vectors may have implications in the design of future gene therapy trials.

It should be remembered the specification merely discloses that mice are administered cationic liposomes/plasmid DNA in gene delivery assays. See pages 24-27 of the instant specification. There is no indication as to what genetic condition or

disorder the mice used in the gene delivery assays were suffering from. Thus, there was no indication that a genetic disorder or condition was being treated. The specification has failed to teach or disclose the claimed method.

C) The declaration submitted by Dr. Keller under 37 CFR 1.132 filed March 31, 2006 is insufficient to overcome the rejection of claims 23-70 under 35 U.S.C. 112, first paragraph as set forth in the last Office action; the declaration does not provide evidence that the administration of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group can be used to treat genetic disorders or conditions in subjects that are in need of such treatments.

To address the declaration submitted by Dr. Keller, it should be noted that the declaration merely discloses that reporter gene assays may be used to assess therapeutic potential by measuring CAT expression at the time the invention was made. It should be remembered that the claimed invention is directed to method of treating a genetic disorder or disease. There is no evidence (via working examples) in the instant specification or the cited art from Applicant that demonstrates the administration of a compound comprising a cholesterol group or derivative thereof having linked thereto a head group, wherein the head group is more positive than the head group of DC-Chol; further wherein the head group is a straight chain polyamine, further wherein two or more of the amine groups of the polyamine group are separated by an ethylene group to a patient in need of treatment for a genetic disease or disorder which results in the treatment of said patient against the genetic disorder or condition. The cited art merely

disclose the transfection ability of liposome/plasmid DNA compounds and suggest that they may have therapeutic potential.

In view of all of the above, the rejection under 112, first paragraph is maintained.

Status of Claims

5. No claims allowed.

Conclusion

6. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday –Thursday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Jeffery Siew can be reached at (571) 272-0787.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

VLF

Vanessa L. Ford
Biotechnology Patent Examiner
December 10, 2006

NITA MINNIFIELD
PRIMARY EXAMINER